Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

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This table lists the known, predicted, or suspected pharmacokinetic (PK) interactions between drugs used for the treatment or prevention of HIV-associated opportunistic infections (OIs). Many of the drugs listed in this table may also interact with antiretroviral (ARV) drugs. Clinicians should refer to the Drug–Drug Interactions tables in the most current Adult and Adolescent Antiretroviral Guidelines to assess interaction potentials between OI drugs and ARV drugs.

Throughout the table, three recommendations are commonly used when concomitant administration of two drugs may lead to untoward consequences. The rationales for these recommendations are summarized below:

Do not coadminister.

There is either strong evidence or strong likelihood that the PK interaction cannot be managed with a dose modification of one or both drugs and will or may result in either—

- Increase in concentrations of one or both drugs, which may lead to excessive risk of toxicity; *or*
- Decrease in concentrations of one or both drugs, which may render one or both drugs ineffective.

Coadministration should be avoided, if possible.

There is a potential for significant PK interactions. If other more favorable options exist, clinicians are advised to consider changing components of the regimen to accommodate a safer or more effective regimen. However, coadministration of the drugs may be necessary when there are no other acceptable therapeutic options that provide a more favorable benefit-to-risk ratio. Therapeutic drug monitoring (TDM), if available, may facilitate any necessary dose adjustments.

Use with caution.

Drug combinations are recommended to be used with caution when—

- PK studies have shown a moderate degree of interaction of unknown clinical significance; *or*
- Based on the known metabolic pathway of the two drugs, there is a potential for PK interaction of unknown clinical significance.

Rifamycin-Related Induction Interactions

Rifamycin antibiotics are potent inducers of Phase 1 and Phase 2 drug-metabolizing reactions. They also affect various transporters. When a rifamycin antibiotic must be combined with an interacting drug, close monitoring for clinical efficacy of the coadministered agent is advised. TDM, if available, may facilitate any necessary dose adjustments.

- *Rifampin (also known as rifampicin):* Interactions may not be apparent in the first several days of rifampin therapy. However, with daily doses of rifampin, enzyme induction increases over a week or more. Based on

limited data, larger daily doses of rifampin (e.g., 1,200 mg or more) appear to produce about the same maximum induction as lower doses, but the induction effect occurs more rapidly.[1,2]

- *Rifabutin:* In general, rifabutin as a cytochrome P450 (CYP) 3A4 inducer is about 40% of the potency of rifampin, but this can vary by substrate and enzymatic reaction.[3] Rifabutin is also a substrate of CYP3A4 (unlike rifampin and rifapentine) and may be subject to changes in drug exposure when given concomitantly with 3A4 inhibitors or inducers. When used with interacting drug(s), rifabutin dosage modification, TDM, and/or more frequent monitoring for rifabutin-related toxicities may be needed.
- *Rifapentine:* In general, daily rifapentine is at least as potent an inducer as rifampin. However, the potential for drug interactions with once-weekly rifapentine is not well studied. Reduced exposure of concurrent drugs that are CYP3A4 substrates is likely to occur with once-weekly rifapentine, with the extent varying by drug.

Following discontinuation of rifamycins, the enzyme induction effects gradually diminish over time and vary depending on the drug's half-life, the time required to achieve maximal induction, and the degradation course of upregulated enzymes. Generally, after five half-lives, a drug is substantially eliminated from the body. Though rifampin has a short plasma half-life (3–5 hours), de-induction largely depends on the decay time of enzymes produced.[4,5] A 2-week interval after the final dose of rifampin was found sufficient for enzyme levels to return to baseline.[4] Rifapentine and rifabutin, characterized by longer half-lives (approximately 13 and 45 hours, respectively), may exhibit a more prolonged de-induction period than rifampin. Notably, rifabutin induces enzymes to a lesser extent than rifampin and rifapentine, necessitating a shorter de-induction phase.

Azole- and Macrolide-Related Inhibition Interactions

Azole antifungals—including fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole—are substrates and potent inhibitors of metabolic pathways, including CYP enzymes and/or drug transporters (e.g., p-glycoprotein). Interactions involving azole antifungals are common. When an azole antifungal must be combined with an interacting drug, close monitoring for clinical toxicity and efficacy of the azole and/or the coadministered agent may be needed. TDM, if available, may facilitate any necessary dose adjustments.

The newer azole antifungal oteseconazole is less prone to cause clinically significant drug–drug interactions. Oteseconazole does not undergo significant metabolism, and its drug interaction profile is limited to its ability to inhibit the Breast Cancer Resistance Protein (BCRP). Concomitant use of oteseconazole and BCRP substrates may increase the exposure of BCRP substrates.

Macrolides have been shown to form complexes with drug-oxidizing enzymes, including CYP enzymes, which render an inhibitory effect. In general, erythromycin and clarithromycin are moderate to strong inhibitors, whereas azithromycin's propensity for causing clinically relevant drug interactions is the lowest, as it does not form complexes with CYP enzymes that lead to enzyme inactivation.

Pharmacodynamic Interactions

Pharmacodynamic interactions are not addressed in this table. For example, many of the drug classes listed below independently possess a risk for QTc prolongation, including azoles, macrolides, and certain anti-tuberculosis and antimalarial medications. Coadministration of drugs in these classes may require monitoring for QTc prolongation, particularly in patients with predisposing risk factors.

Therapeutic Drug Monitoring

Drug interactions can alter oral absorption or systemic clearance of drugs. More than one interaction can occur at the same time, with potentially opposing effects. TDM, if available, may facilitate any necessary dose adjustments when

interacting drugs are coadministered. TDM allows the clinician to make informed, individualized decisions about dose adjustments that are more precise than standardized dose adjustments based upon anticipated, average effects. When available, "therapeutic ranges" are based on dose-ranging studies that have evaluated clinical outcomes. These ranges are proven to be predictive of efficacy or toxicity. When such data are not available, "normal ranges" are used to represent the drug exposure generally achieved with a standard dose of a drug. Excursions from "normal concentrations" might be associated with decreased efficacy (low concentrations) or increased toxicity (high concentrations), but specific data proving these risks are lacking. In such situations, clinicians should weigh the potential risks and benefits based upon TDM data. Consultations with experts for those drugs may be helpful.

TDM may be particularly useful in the following situations:

- Inadequate therapeutic response
- Overt toxicity
- Risk of serious drug–drug interactions
- Impaired drug absorption

In these cases, TDM can confirm the adequacy of the doses or suggest alternative doses that might lead to superior outcomes.

When TDM is desired, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution. Drugs in this table that are known to have assays (for clinical and/or research purposes) available within the United States and typically in Europe include the following:

- Atovaquone
- Bedaquiline
- Chloroquine
- Clarithromycin
- Dapsone
- Doxycycline
- Fluconazole
- Isavuconazole
- Itraconazole
- Linezolid
- Mefloquine
- Posaconazole
- Quinine
- Rifabutin
- Rifampin
- Rifapentine
- Sofosbuvir
- Tenofovir
- Voriconazole

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Note: To avoid redundancy, drug–drug interactions are listed only once by primary drug (listed alphabetically). Subsequently, when an interacting agent becomes the primary drug, guideline users are referred to the entry for the initial primary drug. See the Clarithromycin row for the first example of this format.

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether/ Lumefantrine	Clarithromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ lumefantrine possible	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Isavuconazole	↑ lumefantrine possible	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Itraconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Mefloquine	↓ lumefantrine possible	If mefloquine is administered immediately before artemether/lumefantrine, monitor for decreased efficacy of artemether/lumefantrine and encourage food intake.
	Posaconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Rifabutin[a]	↓ artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.
	Rifampin[a]	Artemether AUC ↓ 89% DHA AUC ↓ 85% Lumefantrine AUC ↓ 68%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ artemether, DHA, and lumefantrine expected	Do not coadminister.

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	Voriconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
Atovaquone	Doxycycline	Atovaquone concentration ↓ approximately equal to 40% with tetracycline No interaction study with doxycycline	Dose adjustment not established; if coadministered, instruct patient to take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifabutin[a]	Atovaquone C_{ss} ↓ 34% Rifabutin C_{ss} ↓ 19%	Dose adjustment not established; if coadministered, instruct patient to take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifampin[a]	Atovaquone C_{ss} ↓ 52% Rifampin C_{ss} ↑ 37%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ atovaquone expected	Do not coadminister.
Bedaquiline	Clarithromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ bedaquiline possible	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Isavuconazole	↑ bedaquiline possible	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Itraconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities. If coadministration is required for >14 days, weigh the benefits of therapy against the risks of bedaquiline toxicities.

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	Posaconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Rifabutin[a]	↔ bedaquiline ↓ rifabutin possible	If coadministered, separate time of administration; perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	Bedaquiline AUC ↓ 53%	Do not coadminister.
	Rifapentine[a]	Daily Rifapentine Bedaquiline AUC ↓ 55% Weekly Rifapentine ↓ bedaquiline expected	Do not coadminister.
	Voriconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
Brincidofovir	Clarithromycin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone clarithromycin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone erythromycin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities. Consider azithromycin in place of erythromycin.
	Rifampin[a]	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone rifampin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities.
Caspofungin	Rifabutin[a]	↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).

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	Rifampin[a]	Caspofungin C_{min} ↓ 30%	If coadministered, caspofungin dose should be increased to 70 mg/day. Consider alternative echinocandin (e.g., micafungin or anidulafungin).
	Rifapentine[a]	Daily Rifapentine ↓ caspofungin expected Weekly Rifapentine ↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).
Chloroquine	Clarithromycin	↑ chloroquine expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ chloroquine expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Isavuconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Itraconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Posaconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Rifabutin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifampin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ chloroquine expected	Monitor for chloroquine efficacy.
	Voriconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
Clarithromycin	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.

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Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Fluconazole	Clarithromycin AUC ↑ 18% and C_{min}↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	↑ isavuconazole and clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of both isavuconazole and clarithromycin. Role of isavuconazole TDM has not been established.
	Itraconazole	↑ itraconazole and clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of both itraconazole and clarithromycin; perform itraconazole and clarithromycin TDM and adjust dose accordingly.
	Mefloquine	↑ mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for mefloquine toxicity.
	Posaconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of clarithromycin; perform clarithromycin TDM and adjust dose accordingly.
	Quinine	↑ quinine expected ↑ clarithromycin possible	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Rifabutin[a]	Clarithromycin AUC ↓ 44% 14-OH clarithromycin AUC ↑ 57% Rifabutin AUC ↑ 76% to 99% des-rifabutin AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, consider reducing rifabutin dose, perform clarithromycin and rifabutin TDM and adjust dose accordingly. Monitor for rifabutin toxicities.

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	Rifampin[a]	Clarithromycin concentration ↓ 87% Rifampin AUC ↑ 60%	Do not coadminister. Use azithromycin in place of clarithromycin.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ clarithromycin expected ↑ 14-OH clarithromycin and rifapentine expected	Daily Rifapentine Do not coadminister. Use azithromycin in place of clarithromycin. Weekly Rifapentine Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for rifapentine toxicities and clarithromycin efficacy; perform clarithromycin and rifapentine TDM and adjust doses accordingly.
	Voriconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of clarithromycin; perform clarithromycin TDM and adjust dose accordingly.
Dapsone	Rifabutin[a]	Dapsone AUC ↓ 27% to 40%	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
	Rifampin[a]	Dapsone concentration ↓ sevenfold to tenfold and $t_{1/2}$ ↓ from 24 hours to 11 hours	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ dapsone expected	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
Doxycycline	Atovaquone	See Atovaquone.	See Atovaquone.
	Rifabutin[a]	↓ doxycycline possible	Monitor closely for doxycycline efficacy or consider alternative therapy.

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	Rifampin[a]	Doxycycline AUC ↓ 59%	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
	Rifapentine[a]	Daily Rifapentine ↓ doxycycline expected Weekly Rifapentine ↓ doxycycline possible	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
Erythromycin	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Fluconazole	↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	↑ erythromycin and isavuconazole possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Itraconazole	Itraconazole AUC ↑ 36% ↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ mefloquine possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Posaconazole	↑ erythromycin expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Quinine	↑ quinine expected ↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Rifabutin[a]	↓ erythromycin possible ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy and rifabutin toxicities; perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	↓ erythromycin expected	Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy.

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	Rifapentine[a]	Daily and Weekly Rifapentine ↓ erythromycin expected	Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy.
	Voriconazole	↑ erythromycin expected	Do not coadminister. Consider azithromycin in place of erythromycin.
Fluconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ fluconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and fluconazole toxicity.
	Rifabutin[a]	Rifabutin AUC ↑ 80% ↔ fluconazole expected	Use with caution. Monitor for rifabutin toxicities. Perform rifabutin TDM; may need to decrease rifabutin dose to 150 mg/day.
	Rifampin[a]	Fluconazole AUC ↓ 23% to 56%	Monitor for antifungal efficacy; may need to increase fluconazole dose.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ fluconazole expected	Monitor for antifungal efficacy; may need to increase fluconazole dose.
Glecaprevir/ Pibrentasvir	Rifabutin[a]	↓ glecaprevir and pibrentasvir possible	Coadministration should be avoided, if possible. Consider alternative agents.
	Rifampin[a]	Glecaprevir AUC ↓ 88% Pibrentasvir AUC ↓ 87%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ glecaprevir and pibrentasvir expected	Do not coadminister. Consider alternative agents.
	TDF	TFV AUC ↑ 29% when coadministered as EFV/TDF/FTC	Use usual dose. Monitor renal function or consider TAF.

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	TAF	↔ TFV concentration when coadministered as EVG/c/TAF/FTC	No dose adjustment necessary.
Ibrexafungerp	Clarithromycin	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Erythromycin	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Itraconazole	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Posaconazole	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Rifabutin[a]	↓ Ibrexafungerp expected	Do not coadminister.
	Rifampin[a]	↓ Ibrexafungerp expected	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ Ibrexafungerp expected	Do not coadminister.
	Voriconazole	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
Isavuconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ isavuconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and isavuconazole toxicities.
	Rifabutin[a]	↓ isavuconazole expected ↑ rifabutin expected	Consider alternative agent(s). If alternative agents are not available, use with close monitoring for isavuconazole antifungal activity and rifabutin toxicity. Perform rifabutin and isavuconazole TDM and adjust dose accordingly.

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	Rifampin[a]	Isavuconazole AUC ↓ 97%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ isavuconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Itraconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Mefloquine	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ itraconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and itraconazole toxicities; perform itraconazole TDM and adjust dose accordingly.
	Rifabutin[a]	Itraconazole AUC ↓ 70% ↑ rifabutin expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifampin[a]	Itraconazole AUC ↓ 64% to 88%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ itraconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Linezolid	Rifabutin[a]	↓ linezolid possible	Monitor for linezolid efficacy.
	Rifampin[a]	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly.
	Rifapentine[a]	Daily Rifapentine ↓ linezolid expected	Daily Rifapentine Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly.

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Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
		Weekly Rifapentine ↓ linezolid possible	Weekly Rifapentine Monitor for linezolid efficacy.
Mefloquine	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Posaconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Rifabutin[a]	↓ mefloquine possible	Monitor for mefloquine efficacy.
	Rifampin[a]	Mefloquine AUC ↓ 68%	Do not coadminister. Use alternative antimalarial drug or rifabutin.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ mefloquine expected	Do not coadminister. Use alternative antimalarial drug or rifabutin.
	Voriconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
Posaconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	↑ quinine expected ↑ posaconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifabutin[a]	Posaconazole AUC ↓ 49% Rifabutin AUC ↑ 72%	Coadministration should be avoided, if possible. If coadministered, perform posaconazole and rifabutin TDM and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities.
	Rifampin[a]	↓ posaconazole expected	Do not coadminister when treating invasive fungal infections. If coadministered for treatment of noninvasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ posaconazole expected	Daily Rifapentine Do not coadminister when treating invasive fungal infections. If coadministered for treatment of noninvasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response. Weekly Rifapentine Coadministration should be avoided, if possible. If coadministered, perform posaconazole TDM and adjust dose accordingly; monitor clinical response.
Quinine	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Rifabutin[a]	↓ quinine possible ↑ rifabutin possible	Monitor for quinine efficacy. Monitor for rifabutin toxicity.
	Rifampin[a]	Quinine AUC ↓ 75% to 85%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ quinine expected	Do not coadminister.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	↑ quinine expected	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.
Rifabutin[a]	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Sofosbuvir/Velpatasvir	↓ velpatasvir, sofosbuvir expected	Do not coadminister.
	Tedizolid	↓ tedizolid possible	Monitor for tedizolid efficacy.
	TAF	↓ TAF, TFV, TFV-DP expected ↑ TFV-DP expected versus TDF alone	If coadministered, monitor for HIV and HBV treatment efficacy. Note: Interpretation extrapolated from TAF and rifampin (see Rifampin). FDA labeling recommends not to coadminister.
	TDF	↔ TDF, TFV, TFV-DP expected	No dosage adjustment necessary.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	Voriconazole AUC ↓ 79% Rifabutin AUC ↑ 4-fold	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s). Coadministration may be considered if both voriconazole and rifabutin TDM are available to guide therapy.
Rifampin[a]	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Sofosbuvir/Velpatasvir	Sofosbuvir AUC ↓ 72% Velpatasvir AUC ↓ 82%	Do not coadminister.
	Tedizolid	Tedizolid AUC ↓ 20%	Monitor for tedizolid efficacy.
	TAF	TAF Plus Rifampin • TAF AUC ↓ 55% • TFV AUC ↓ 54%	If coadministered, monitor for HIV and HBV treatment efficacy.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
		• TFV-DP AUC ↓ 36% Intracellular TFV-DP concentration is 4.2-fold greater than with TDF alone.	Note: FDA labeling recommends not to coadminister.
	TDF	TDF Plus Rifampin 600 mg Daily ↔ TFV	No dosage adjustment necessary
	Voriconazole	Voriconazole AUC ↓ 96%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Rifapentine[a]	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Tedizolid	Daily Rifapentine ↓ tedizolid expected Weekly Rifapentine ↓ tedizolid possible	Daily or Weekly Rifapentine Monitor for tedizolid efficacy.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	TAF	Daily and Weekly Rifapentine ↓ TAF, TFV, TFV-DP possible	If coadministered, monitor for HIV and HBV treatment efficacy. Note: FDA labeling recommends not to coadminister.
	TDF	↔ TDF, TFV, TFV-DP expected	No dosage adjustment necessary
	Sofosbuvir/Velpatasvir	↓ sofosbuvir, velpatasvir expected	Do not coadminister.
	Voriconazole	↓ voriconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Sofosbuvir/ Velpatasvir	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	TAF	TFV AUC ↑ 79% (when RPV/TAF/FTC given with SOF/VEL/VOX) TFV AUC ↑ 67% (when BIC/TAF/FTC given with SOF/VEL/VOX)	No dosage adjustment necessary.
	TDF	TFV AUC ↑ 35% to 40% (when given with EVG/c/FTC or RPV/FTC) TFV AUC ↑ 81% (when given with EFV/FTC and SOF/VEL) TFV AUC ↑ 39% (when given with DRV/r/FTC and SOF/VEL/VOX)	Monitor for TDF toxicities. Consider TAF in place of TDF.
Tedizolid	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
Tenofovir Alafenamide	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Tenofovir Disoproxil Fumarate	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
Voriconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	See Quinine.	See Quinine.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.

[a] Refer to the subsection Rifamycin-Related Induction Interactions in the Table 4 introduction above.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: 14-OH = active metabolite of clarithromycin; AUC = area under the curve; BIC = bictegravir; C_{min} = minimum concentration; C_{ss} = concentration at steady state; DHA = dihydroartemisinin; DRV/r = darunavir/ritonavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; RPV = rilpivirine; SOF = sofosbuvir; $t_{1/2}$ = half-life; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TFV= tenofovir; TFV-DP = tenofovir diphosphate; VEL = velpatasvir; VOX = voxilaprevir

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

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